EXHIBIT 1

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND ADDICTION PRODUCTS

MEMORANDUM

DATE: May 13, 2019

FROM: Ning Hu, MD MS
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THROUGH Pamela Horn, MD
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TO: Chair, Members and Invited Guests
Drug Safety and Risk Management Advisory Committee (DSaRM)
Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC)

RE: Opioids Regulatory Background for the June 11-12, 2018, DSaRM/AADPAC Meeting

Background

Opioid analgesic products present unique challenges in clinical practice and public health in that they provide clinically significant analgesic benefit, including for pain for which other analgesics are inadequate, while also carrying serious risks including sedation and respiratory depression. Overdose of an opioid analgesic can result in death. The misuse and abuse of prescription opioids and the associated risks of addiction, overdose, and death are currently a major public

health crisis in the United States.

Unlike other approved analgesic products, most opioid analgesics have no maximum dose because there is no ceiling effect for analgesia. Further, along the range of doses that have been used clinically, no particular dose of any opioid has been determined to be a cutoff point between safe-for-use or unsafe-for-use. The higher the dose, the greater the analgesic effect. However, it is also true that the higher the dose, the greater the risk for serious adverse events.

Physiologic responses to exposure to opioid analgesics include the development of tolerance and physical dependence. These two physiologic processes can complicate the management of patients on opioid analgesics when not recognized and taken into consideration when evaluating each patient. In the setting of chronic pain, over time some patients may require increases in their dose to maintain efficacy, resulting in relatively high doses of opioids. This may be due to the development of tolerance but may also be due to worsening in the underlying pain, or in some cases, the development of opioid-induced hyperalgesia.

Because of the societal harms associated with the over reliance on the use of prescription opioid analgesics, many aspects of the use of opioid analgesics have come under intense scrutiny.

It is important to consider the potential repercussions of well-meaning attempts to address the opioid crisis without adequate scientific evidence to support such actions. Inadequately treated chronic pain has consequences, and in general, the use of higher doses of opioid analgesics often occurs in the setting of chronic pain, as patients titrate to an effective dose. Robust evidence supports that chronic pain itself, regardless of type, is an important independent risk factor for suicidality, as chronic pain patients are at least twice as likely to report suicidal behaviors or to complete suicide.[1] In a national sample of Veterans Health Administration, among patients discontinued from long-term opioid therapy for chronic pain, nearly 12% had documented suicidal ideation and suicidal self-directed violence in the year following discontinuation.[2]

Further, it has been pointed out that rapid forced opioid tapering can destabilize patients with chronic pain, precipitating severe opioid withdrawal accompanied by worsening pain and profound loss of function. To escape the resultant suffering, some patients may seek relief from illicit (and inherently more dangerous) sources of opioids, whereas others may become acutely suicidal.[3]

In support of the idea that there should be absolute limits on the total daily dose of opioid analgesics, many have inappropriately turned to the CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016.[4] The idea behind this guideline was that "improving the

[1] Racine, M. Chronic pain and suicide risk: A comprehensive review. Progress in Neuropsychopharm and Biological Psychiatry 2018; 87:269-280

[2] Demidenko MI, et. al., Suicidal ideation and suicidal self-directed violence following clinician-initiated prescription opioid discontinuation among long-term opioid users, General Hospital Psychiatry 47 (2017) 29–35

[3] International Stakeholder Community of Pain Experts and Leaders Call for an Urgent Action on Forced Opioid Tapering. Pain Medicine. 2019;20: 429-433

[4] https://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fmmwr%2Fvolumes%2F65%2Frr%2Frr6501e1er.htm

way opioids are prescribed through clinical practice guidelines can ensure patients have access to safer, more effective chronic pain treatment while reducing the number of people who misuse or overdose from these drugs."[5] However, the guidelines were misinterpreted and misapplied, contributing to substantial harms to patients, particularly patients with chronic pain who were forced to taper their previously stable opioid doses to lower doses, or who were forced to discontinue their opioids through forced tapers or patient abandonment. This was captured in a recent statement by the CDC, "CDC Advises Against Misapplication of the *Guideline for Prescribing Opioids for Chronic Pain*".[6] Based on the extent of misapplication that has taken place, and resultant harms, it is worthwhile to note the following key points taken verbatim from this statement:

CDC is raising awareness about the following issues that could put patients at risk:

- **Misapplication of recommendations to populations outside of the Guideline's scope.** The Guideline is intended for primary care clinicians treating chronic pain for patients 18 and older. Examples of misapplication include applying the Guideline to patients in active cancer treatment, patients experiencing acute sickle cell crises, or patients experiencing post-surgical pain.
- **Misapplication of the Guideline's dosage recommendation that results in hard limits or "cutting off" opioids.** The Guideline states, "*When opioids are started*, clinicians should prescribe the lowest effective dosage. Clinicians should… avoid *increasing* dosage to ≥90 MME/day or carefully justify a decision to titrate dosage to ≥90 MME/day." The recommendation statement does not suggest discontinuation of opioids already prescribed at higher dosages.
- **The Guideline does not support abrupt tapering or sudden discontinuation of opioids**. These practices can result in severe opioid withdrawal symptoms including pain and psychological distress, and some patients might seek other sources of opioids. In addition, policies that mandate hard limits conflict with the Guideline's emphasis on individualized assessment of the benefits and risks of opioids given the specific circumstances and unique needs of each patient.
- **Misapplication of the Guideline's dosage recommendation to patients receiving or starting medication-assisted treatment for opioid use disorder.** The Guideline's recommendation about dosage applies to use of opioids in the management of chronic pain, not to the use of medication-assisted treatment for opioid use disorder. The Guideline strongly recommends offering medication-assisted treatment for patients with opioid use disorder.

On May 9 and 10, 2019, the Best Practices in Pain Management Task Force met to finalize consensus on the "Draft Report on Pain Management Best Practices: Updates, Gaps, Inconsistencies, and Recommendations."[7] The Comprehensive Addiction and Recovery Act (CARA) of 2016 led to the creation of the Pain Management Best Practices Inter-Agency Task

[5] https://www.cdc.gov/drugoverdose/prescribing/guideline.html
[6] https://www.cdc.gov/media/releases/2019/s0424-advises-misapplication-guideline-prescribing-opioids.html
[7] https://www.hhs.gov/ash/advisory-committees/pain/meetings/2019-05-09/index.html

Force whose mission has been to determine whether gaps in or inconsistencies between best practices for acute and chronic pain management exist and to propose updates and recommendations to those best practices. The recommendations of the Task Force will be finalized and submitted to Congress in 2019.

Some of the strengths of this report include the use of 29 clinical and academic experts with decades of experience in the fields of pain management, patient advocacy, substance use disorders, and mental health; and the open, public nature of the report, its deliberations, and opportunity to receive and receive patient testimonials and public meeting comments, including approximately 6,000 comments from the public submitted during a 90-day public comment and 3,000 comments from 2 public meetings. Relevant to the topic at hand, the task force did not recommend any absolute limits on the individual dose or total daily dose of opioid analgesics. Rather, the task force concluded that emphasis should be placed on the importance of individualized care, the use of multimodal approaches to acute pain management, and the use of multidisciplinary approaches to chronic pain management. The executive summary of this report has been appended to this memo.

This meeting presents an opportunity to examine whether the role of higher dose opioids for chronic painful conditions in the outpatient setting is warranted.

The following are definitions of important terms related to opioid analgesics.

- Analgesic tolerance is the need for increasing doses of opioids to maintain a defined analgesic effect[8] (in the absence of disease progression or other external factors). It exhibits a wide individual variability during opioid therapy.

- Physical dependence results in a physical disturbance (withdrawal symptoms) after abrupt discontinuation or a significant dosage reduction of a drug[9].

  Tolerance and physical dependence are physiological changes that develop during chronic opioid therapy. Abuse and addiction are separate and distinct from physical dependence and tolerance.

- Addiction[10] is a primary, chronic disease of brain reward, motivation, memory and related circuitry. Dysfunction in these circuits leads to characteristic biological, psychological, social and spiritual manifestations. This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors.

  Addiction is characterized by inability to consistently abstain, impairment in behavioral control, craving, diminished recognition of significant problems with one's behaviors and interpersonal relationships, and a dysfunctional emotional response. Like other chronic diseases, addiction often involves cycles of relapse and remission. Without treatment or

[8] Opioid analgesic products labeling, such as OxyContin (NDA 22272), Hysingla ER (206627), etc. Section 9, "DRUG ABUSE AND DEPENDENCE"
[9] Ibid.
[10] American Society of Addiction Medicine. Public Policy Statement: Definition of Addiction. Short Definition of Addiction.

engagement in recovery activities, addiction is progressive and can result in disability or premature death.

- Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects.[11]

These phenomena are separate and distinct. Having developed tolerance and physical dependence to opioids is not the same as having an addiction to opioids and can develop in the absence of abuse or addiction. Conversely, addiction may not always be accompanied by concurrent tolerance and symptoms of physical dependence. In addition, abuse of opioids can occur in the absence of addiction.

Chronic pain is defined as ongoing or recurrent pain that lasts beyond the usual course of acute illness or injury healing and adversely affects an individual's well-being. Pain is typically considered chronic when it lasts more than three months in duration.

Opioid Analgesic Products for Outpatient Use

FDA has approved a variety of extended-release/long-acting (ER/LA) and immediate-release (IR) opioid analgesics and combination opioid/non-opioid products for outpatient use. The product labeling contains a summary of the essential scientific information needed for the safe and effective use of the drug. The following information is included in opioid product labeling:

- Indications

  The primary role of the INDICATIONS AND USAGE section of labeling for opioid analgesics is to enable health care practitioners to readily identify appropriate therapies for the context of use. In opioid analgesic labeling, ER/LA opioid products are indicated for management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate, and the IR opioid products are indicated for management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. The indications are worded this way to alert the prescriber that opioids should be used when alternatives have not or are not expected to be adequate for the pain that the patient is experiencing to better balance the benefit-risk profile of the opioid analgesic.

- Conversion information and equianalgesic doses

  The purpose of opioid conversion information in the product labeling is to enable pain management practitioners to safely convert a patient from an existing opioid regimen to another and not to facilitate equianalgesic conversion.

[11] Opioid analgesic products labeling, such as OxyContin (NDA 22272), Hysingla ER (206627), etc. Section 9, "DRUG ABUSE AND DEPENDENCE"

Conversion information and conversion factors are included in the DOSAGE AND ADMINISTRATION section in opioid products' labeling. The conversion information is based on the clinical trial data for the specific product and attempts to account for incomplete cross-tolerance among different opioid products. For this reason, the information should only be used to convert to the specific opioid for which the label was written from the other opioid products listed.

The conversion information/factors in product labeling neither describes equianalgesic conversion (the dose at which two analgesics (at steady state) provide approximately the same pain relief[12]) nor suggests that the doses will have the same adverse reactions or euphoric effects. Equianalgesic ratios are difficult to establish because multiple factors can influence the accurate estimation of analgesia, such as incomplete cross-tolerance among different opioid products, wide individual variability in opioid tolerance due to genetic factors, and previous opioid use.

- Tolerance criteria and requirements

  Because of the wide variability of individual tolerance, the opioid product labeling recommends a conservative approach when determining the initial and total daily dosage of the drug based on the patient's level of tolerance. High dosage strengths and high total daily dose (TDD) are only for use in opioid-tolerant patients. Based on clinical trial data, a practical definition for opioid tolerant has been developed. In this context, patients who are opioid tolerant are those receiving, for one week or longer, at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl per hour, 30 mg oral oxycodone per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid.

  Some opioid products are only indicated for use in opioid-tolerant patients. With the consideration of individual variability, the clinician may individually titrate the drug to a dose that provides adequate analgesia and minimizes adverse reactions based on the patient's response.

Extended release/long-acting (ER/LA) opioid analgesic products

A summary of extended release/long-acting (ER/LA) opioid products is shown in Table 1. ER/LA opioid products are approved with the indication of management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Nucynta ER (Tapentadol, NDA 200533) is further indicated for the treatment for neuropathic pain associated with diabetic peripheral neuropathy (DPN). ER/LA opioids are not limited to a maximum daily dose based on their activity at the opioid receptor because opioids have neither a ceiling effect nor uniform therapeutic plasma levels. The general approach is to initiate opioid treatment with a low dose and individually titrate to a tolerable dose that provides adequate analgesia. The products that have a maximum daily dose (MDD) defined

[12] Shaheen, Philip E et al. "Opioid Equianalgesic Tables: Are They All Equally Dangerous?" Journal of pain and symptom management. 38.3 409–417. Web.

are Nucynta ER (Tapentadol, NDA 200533) and Conzip (Tramadol, NDA 22370) given their possible combined mechanism of action of mu-opioid receptor (MOR) agonist and serotonin/norepinephrine reuptake inhibitor (SSRI/NRI) and the dose-response relationship for toxicity with respect to the SSRI/NRI activity and Butrans (buprenorphine, NDA 21306 and Belbuca (buprenorphine, NDA 207932) based on the potential for QTc interval prolongation. Duragesic (Fentanyl Citrate, NDA 19813) and Exalgo (Hydromorphone Hydrochloride, NDA 21217) are only indicated for use in opioid-tolerant patients.

Table 1. Extended-release/long-acting (ER/LA) opioid products

Product name NDA# Date of approval	API	Dosage forms Formulation/route Strengths	Dosing regimen Dosage and administration based on opioid tolerance[a]
Butrans 21306 06/30/2010	Buprenorphine	• Transdermal system • 5 mcg, 7.5 mcg, 10 mcg, 15 mcg, 20 mcg/hour	• 7.5, 10, 15, and 20 mcg/hour are only for use in opioid-experienced[b] and tolerant patients • Opioid-naïve patients: initiate with a 5 mcg/hour patch. • MDD 20 mcg/hour based on potential for QT interval prolongation
Belbuca 207932 10/23/2015	Buprenorphine Hydrochloride	• Buccal film • 75 mcg, 150 mcg, 300 mcg, 450 mcg, 600 mcg, 750 mcg, and 900 mcg	• For opioid-naïve patients: 75 mcg once daily or q12h • 600 mcg, 750 mcg, and 900 mcg are only for use following titration • MDD 900 mcg q12h based on potential for QT interval prolongation
Duragesic 19813 08/07/1990	Fentanyl Citrate	• Transdermal system • 12 mcg, 25 mcg, 37.5 mcg, 50 mcg, 75 mcg and 100 mcg/hour	• For opioid-tolerant patients only • Each transdermal system is intended to be worn for 72 hours
Zohydro ER 202880 10/25/2013	Hydrocodone Bitartrate	• Oral capsules • 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, and 50 mg	• A single dose > 40 mg, or TDD > 80 mg are only for use in opioid tolerant patients • For opioid-naïve and opioid non-tolerant patients: start 10 mg q12h
Hysingla ER[c] 206627 11/20/2014	Hydrocodone Bitartrate	• Oral tablets • 20 mg, 30 mg, 40 mg, 60 mg, 80 mg, 100 mg, and 120 mg	• TDD > 80 mg are only for use in opioid tolerant patients • For opioid-naïve patients: initiate with 20 mg q24h
Exalgo[d] 21217 03/01/2010	Hydromorphone Hydrochloride	• Oral tablets • 8 mg, 12 mg, 16 mg, 32 mg	• For opioid-tolerant patients only q24h
Opana ER[e] 21610 06/22/2006	Oxymorphone Hydrochloride	• Oral tablets • 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg	• Opioid-naïve and non-tolerant patients, initiate with 5 mg q12h
Dolophine 6134 08/13/1947	Methadone hydrochloride	• Oral tablets • 5 mg and 10 mg	• Opioid-naïve patients: initiate 2.5 mg every 8 to 12 hours and titrate up no more frequent than every 3 to 5 days
Arymo ER[c] 208603 01/09/2017	Morphine Sulfate	• Oral tablets • 15 mg, 30, mg, 60 mg	• > 60 mg, or a TDD > 120 mg are only for use in opioid-tolerant patients: • For opioid-naïve and opioid non-tolerant patients: start 15 mg q 8 or 12 h
Kadian 20616 07/03/1996	Morphine Sulfate	• Oral capsules • 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 80 mg, 100 mg, 200 mg	• 100 mg or 200 mg tablets daily, a single dose > 60 mg, or a TDD > 120 mg are only for use in opioid-tolerant patients • For opioid-naïve patients: start with IR morphine, then convert to Kadian • For opioid non-tolerant patients: initiate with a 30 mg daily
MS Contin 19516 05/29/1987	Morphine Sulfate	• Oral tablets • 15 mg, 30 mg, 60 mg, 100 mg, 200 mg	• 100 mg and 200 mg tablets, a single dose > 60 mg, or a TDD > 120 mg only are only for use in opioid tolerant patients • For opioid-naïve and non-tolerant patients: initiate with 15 mg every 8 to 12 hours

Embeda[c] 22321 08/13/2009	Morphine Sulfate and Naltrexone Hydrochloride	• Oral capsules • 20 mg /0.8 mg, 30 mg /1.2 mg, 50 mg /2 mg, 60 mg /2.4 mg, 80 mg /3.2 mg, 100 mg /4 mg	• 100/4 mg, single dose of 60 mg/2.4 mg, TDD > 120 mg/5 mg. q24h are only for use in opioid tolerant patients • For Opioid-naïve and opioid non-tolerant patients, initiate with 20 mg/0.8 mg q24h
MorphaBond ER[c] 206544 10/02/2015	Morphine Sulfate	• Oral tablets • 15 mg, 30 mg, 60 mg, 100 mg	• 100mg tablets, a single dose > 60 mg, or a TDD > 120 mg are only for use in opioid tolerant patients • For opioid-naïve and opioid non-tolerant patients: start 15 mg q8h or q12h
OxyContin[cf] 22272 04/05/2010	Oxycodone Hydrochloride	• Oral tablets • 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg.	• 60 and 80 mg, a single dose > 40 mg, or a TDD > 80 mg, q12h are only for use in opioid-tolerant patients • For opioid-naïve and non-tolerant adults: start 10 mg q12h
Xtampza ER[c] 208090 04/26/2016	Oxycodone	• Oral Capsules • 10 mg, 15 mg, 20 mg, 30 mg, 40 mg	• A TDD > 80 mg or a single dose > 40 mg are only for use in opioid-tolerant patients • For opioid-naïve and opioid non-tolerant patients: 10 mg q12h
Nucynta ER[gh] 200533 08/25/2011	Tapentadol	• Oral tablets • 50 mg, 100 mg, 150 mg, 200 mg, 250 mg	• Opioid-naïve and non-tolerant patients: start 50 mg q12h • MDD: 500 mg per day
Conzip ER[g] 22370 Tramadol	Tramadol hydrochloride	• Oral capsules • 100 mg, 200 mg and 300 mg	• For opioid-naïve and opioid non-tolerant patients, start with 100 mg once daily • MDD: 300 mg per day

[a] Patients considered opioid-tolerant are those taking, for one week or longer, at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl per hour, 30 mg oral oxycodone per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid.
[b] Patients who are opioid-experienced are those receiving, for one week or longer, daily opioid doses up to 80 mg/day of oral morphine or an equianalgesic dose of another opioid.
[c] Abuse-deterrent properties are described in labeling
[d] Discontinued and generics available.
[e] Discontinued and generics available; Opana ER NDA 201655 withdrawn for formulation-specific safety reasons.
[f] The Indication also includes opioid-tolerant pediatric patients 11 years of age and older who are already receiving and tolerate a minimum daily opioid dose of at least 20 mg oxycodone orally or its equivalent.
[g] Products that have a MDD defined.
[h] The product is also indicated for neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.
Abbreviations: NDA: new drug application; API: active pharmaceutical ingredient; TDD: total daily dose; MDD: maximum daily dose.

Immediate-release (IR) opioid analgesic products

A summary of immediate-release (IR) opioid analgesic products with approved new drug applications (i.e., non-generic opioid analgesic products) is shown in Table 2. IR oral opioid products are approved with the indication of management of pain severe enough to require an opioid agonist and for which alternative treatments are inadequate. Several products are specifically indicated for the management of "acute pain". A group of transmucosal immediate-release fentanyl (TIRF) products are indicated for management of breakthrough pain in cancer patients 18 years of age and older who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain. Similar to ER/LA opioid

products, most of the IR opioids have no maximum daily dose defined except tapentadol and tramadol products, fixed dose combination products, and TIRF products as detailed in Table 2.

Numerous generic immediate-release (IR) opioid analgesics and combination opioid/non-opioid products are approved for outpatient use in management of pain severe enough to require an opioid agonist and for which alternative treatments are inadequate. Available IR generic opioid products include products with meperidine, levorphanol, tramadol, tapentadol, codeine, hydrocodone, benzhydrocodone, oxycodone, morphine, oxymorphone, hydromorphone, and fentanyl APIs. They are available in single-entity opioids and in combination with non-opioid analgesic drugs including acetaminophen, aspirin, and ibuprofen, butalbital, and caffeine. Some combination opioid/non-opioid products only have generic products available. Those products have a MDD defined due to dose-dependent toxicity of the non-opioid analgesic APIs.

Table 2. Immediate-release (IR) opioid products

Product name NDA# Date of approval	APIs	Dosage forms Formulation/routes Strengths	Dosing regimen Max daily dosing (MDD)
Products for oral route of administration			
Apadaz[a] 208653 2/23/2018	Benz-hydrocodone /APAP	• Oral tablets • 6.12 mg benzhydrocodone (equivalent to 6.67 mg benzhydrocodone hydrochloride) and 325 mg acetaminophen	• 1 or 2 tablets every 4 to 6 hours as needed for pain • MDD: Not exceed 12 tablets in a 24 hour period
Codeine 22402 7/16/2009	Codeine sulfate	• Oral tablets • 15 mg, 30 mg, and 60 mg	• 15 to 60 mg every 4 hours as needed
Codeine 202245 6/30/2011	Codeine sulfate	• Oral solution • 30 mg/5 mL (6 mg/mL)	• Initiate treatment with 15 to 60 mg (2.5 mL to 10 mL) every 4 hours as needed.
Fioricet w/ Codeine 20232 7/30/1992	Codeine/ APAP/butalbital/caffeine	• Oral capsules • 50 mg butalbital, 325 mg acetaminophen, 40 mg caffeine, and 30 mg codeine phosphate	• Initiate treatment with one or two capsules every 4 hours as needed for pain • MDD: Not exceed 6 capsules
Fioricet w/ Codeine 19429 10/26/1990	Codeine/ aspirin/ butalbital/ caffeine	• Oral capsules • 50 mg butalbital, 325 mg aspirin, 40 mg caffeine, and 30 mg • codeine phosphate	• Initiate treatment with one or two capsules every 4 hours. • MDD: Not exceed 6 capsules
Synalgos-DC 11483 7/7/1958	Dihydrocodeine/ aspirin/caffeine	• Oral capsules • 356.4 mg aspirin, 30 mg caffeine, and 16 mg dihydrocodeine bitartrate	• Initiate treatment with two capsules orally every 4 hours as needed for pain
Dilaudid 19891 12/7/1992	Hydromorphone	• Oral solution: 5 mg/5 mL (1 mg/mL) • Oral tablets: 2 mg, 4 mg, and 8 mg	• Oral solution: one-half (2.5 mL) to two teaspoonfuls (10 mL), 2.5 mg to 10 mg, every 3 to 6 hours • Oral tablets: 2 mg to 4 mg, orally, every 4 to 6 hours.
Dilaudid 19892 12/7/1992	Hydromorphone	• Oral solution: 5 mg/5 mL (1 mg/mL) • Oral tablets: 2 mg, 4 mg, and 8 mg	• Oral solution: one-half (2.5 mL) to two teaspoonfuls (10 mL), 2.5 mg to 10 mg, every 3 to 6 hours • Oral tablets: 2 mg to 4 mg, orally, every 4 to 6 hours.

Levo-Dromoran[b] 8720 12/19/1991	Levorphanol	• Oral tablets • 2 mg	• Initiate treatment in a dosing range of 1 to 2 mg every 6 to 8 hours as needed for pain
Demerol 5010 11/10/1942	Meperidine	• Oral tablets: 50 mg and 100 mg • Oral solution: 50 mg/5mL (10 mg/mL)	• Adult Patients: Start with 50 mg to 150 mg every 3 to 4 hours as needed for pain. • Pediatric Patients: Start with 1.1 mg/kg to 1.8 mg/kg orally, up to the adult dose, every 3 or 4 hours as needed for pain
Morphine 22195 3/17/2008	Morphine	• Oral solution • 10 mg per 5 mL (2 mg/mL), 20 mg per 5 mL (4 mg/mL), 100 mg per 5 mL (20 mg/mL)	• 10 to 20 mg every 4 hours as needed.
Morphine 22207 3/17/2008	Morphine	• Oral tablets • 15 mg and 30 mg	• 15 to 30 mg every 4 hours as needed.
Morphine 201517 6/23/2011	Morphine	• Oral solution • 100 mg/5 mL (20 mg/mL)	• 10 mg to 20 mg (0.5 mL to 1 mL) every 4 hours as needed
Roxybond[c] 209777 04/20/2017	Oxycodone hydrochloride	• Oral tablets • 5 mg, 15 mg, 30 mg	• 5 to 15 mg every 4 to 6 hours as needed for pain.
Roxicodone 21011 8/31/2000	Oxycodone	• Oral tablets • 5 mg, 15 mg, 30 mg	• Initiate dosing with a range of 5 to 15 mg every 4 to 6 hours as needed for pain.
Oxycodone 200534 10/20/2010	Oxycodone	• Oral capsules • 5 mg	• Initiate dosing with a range of 5 to 15 mg every 4 to 6 hours as needed for pain
Oxycodone 200535 10/20/2010	Oxycodone	• Oral solution • 5 mg per 5 mL (1 mg/mL), 100 mg per 5 mL (20 mg/mL)	• Initiate dosing with a range of 5 to 15 mg every 4 to 6 hours as needed for pain.
Oxycodone 201194 1/12/2012	Oxycodone	• Oral solution • 5 mg per 5 mL	• Initiate dosing with a range of 5 to 15 mg every 4 to 6 hours as needed for pain.
Oxaydo 202080 6/17/2011	Oxycodone	• Oral tablets • 5 mg and 7.5 mg oxycodone HCl	• For opioid naïve patients, initiate treatment with 5 mg to 15 mg every 4 to 6 hours as needed for pain
Percodan 7337 4/12/1950	Oxycodone/ aspirin	• Oral tablets • Oxycodone Hydrochloride 4.8355 mg/ Aspirin 325 mg	• One tablet every 6 hours as needed for pain • MDD: aspirin should not exceed 4 grams or 12 tablets.
Opana[d] 21611 6/22/2006	Oxymorphone	• Oral tablets • 5 mg and 10 mg	• Initiate treatment with 10 to 20 mg orally every four to six hours
Nucynta 22304 11/20/2008	Tapentadol	• Oral tablets • 50 mg, 75 mg, 100 mg	• Initiate at 50 mg, 75 mg, or 100 mg every 4 to 6 hours • Daily doses > 700 mg on the first day of therapy and 600 mg on subsequent days have not been studied and are not recommended.
Nucynta[d] 203794 10/15/2012	Tapentadol	• Oral solution • 20 mg/mL	• Initiate at 2.5 mL (50 mg), 3.75 mL (75 mg), or 5 mL (100 mg) every 4 to 6 hours • Daily doses greater than 700 mg on the first day of therapy and 600 mg on

			subsequent days have not been studied and are not recommended
Ultram 20281 3/3/1995	Tramadol	• Oral tablets • 50 mg	• Start at 25 mg/day and titrate in 25 mg increments as separate doses every 3 days to reach 100 mg/day • MDD: Not to exceed 400 mg/day
Ultracet[d] 21123 8/15/2001	Tramadol/APAP	• Oral tablets • Tramadol hydrochloride 37.5 mg and acetaminophen 325 mg	• Initiate treatment with two tablets every 4 to 6 hours as needed for pain relief • MDD: 8 tablets per day
Transmucosal immediate-release fentanyl (TIRF)[e]			
Subsys 202788 01/04/2012	Fentanyl	• Sublingual spray • 100 mcg, 200 mcg, 400 mcg, 600 mcg, 800 mcg dosage strengths.	• Initiate treatment with 100 mcg, individually titrate • Wait at least 4 hours between dosing • Limit consumption to four or fewer doses per day once successful dose is found.
Lazanda 22569 06/30/2011	Fentanyl	• Nasal spray • 100 mcg, 300 mcg or 400 mcg fentanyl base in a 5 mL bottle containing 8 sprays	• Initial dose: 100 mcg (single spray into one nostril), individually titrate • Wait at least 2 hours between dosing • No more than four doses per 24 hours
Abstral 022510 01/07/2011	Fentanyl	• Sublingual tablets • 100 mcg, 200 mcg, 300 mcg, 400 mcg, 600 mcg and 800 mcg strengths as fentanyl base	• Initial dose: 100 mcg, individually titrate • No more than two doses per breakthrough pain episode • Wait at least 2 hours between dosing • Limit to treat four or fewer breakthrough pain episodes per day once a successful dose is found
Fentora 21947 09/25/2006	Fentanyl	• Buccal tablets • 100 mcg, 200 mcg, 400 mcg, 600 mcg, and 800 mcg strengths as fentanyl base.	• Initial dose: 100 mcg, individually titrate • Wait at least 4 hours between dosing • No more than two doses per breakthrough pain episode
Actiq[f] 20747 11/04/1998	Fentanyl citrate	• Solid oral transmucosal lozenge • 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg	• Initial dose: 200 mcg. Prescribe an initial supply of six 200 mcg ACTIQ units, individually titrate • No more than two doses per breakthrough pain episode • Wait at least 4 hours between dosing • Limit to four or fewer units per day once successful dose is found

[a] Indicated for the short-term (no more than 14 days) management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.
[b] Discontinued; generics available.
[c] Discontinued. Abuse-deterrent properties are described in labeling.
[d] Indicated for management of acute pain severe enough to require an opioid agonist and for which alternative treatments are inadequate.
[e] Indicated for management of breakthrough pain in cancer patients 18 years of age and older who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.
[f] Indicated for cancer patients 16 years of age and older
Abbreviations: NDA: new drug application; API: active pharmaceutical ingredient; TDD: total daily dose; MDD: maximum daily dose.